Attorney Docket No. 5405-318 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Chilkoti et al.
Application No.: 10/783,054
Filed: February 20, 2004
For: **TUNABLE NONFOULING SURFACE OF OLIGOETHYLENE GLYCOL**

Confirmation No.: 6784
Group Art Unit: 1615
Examiner: Helm, Caralynne E.

Date: August 29, 2011

Mail Stop APPEAL
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Sir/Madam:

This Appeal Brief is hereby filed in accordance with 37 C.F.R. § 41.37, pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed on June 29, 2011, in accordance with 37 C.F.R. § 41.31.

It is not believed that an extension of time and/or additional fee(s) are required. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due may be charged to Deposit Account No. 50-0220.

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on the date below.

Signature: Sarah Abraham Date: August 29, 2011
Typed Name of Person Signing Certificate: Sarah Abraham

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REAL PARTY IN INTEREST

The real party in interest is Duke University, pursuant to the Assignment from the inventors recorded at the U.S. Patent and Trademark Office on November 21, 2005 at reel number 017049 and frame number 0496.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no appeals or interferences that would be affected by the present appeal.

STATUS OF CLAIMS

Claims 1, 10, 17, and 32-50 have been cancelled and Claims 2-9, 11-16, 18-31, and 51-63 are pending in the present application, with Claims 3, 15, 20, 22-27, 52, and 54-59 withdrawn from consideration, pursuant to 37 C.F.R. § 1,142(b), as being drawn to a nonelected species. Each of Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 stand finally rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** (U.S. Patent Application Publication No. 2002/0102405) in view **of Hawker et al.** (U.S. Patent No. 6,413,587), **Zhang et al.** (*Biomaterials* 1998 19:691-700), **Morgan** (U.S. Patent No. 6,325,628), **Allbritton et al.** (U.S. Patent Application Publication No. 2005/0237480), and **Leckband et al.** (*Journal of Biomaterials Science Polymer Edition* 1999 10:1125-1147). Further, each of Claims 8 and 28 stand finally rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** in view of **Hawker et al., Zhang et al., Morgan, Allbritton et al.**, and **Leckband et al.** and further in view of **Guan et al.** (U.S. Patent No. 6,071,980). Thus, all presently pending claims are currently on appeal. The attached Claims Appendix presents the pending claims as they currently stand following entry of Appellant's Response of January 18, 2011.

STATUS OF AMENDMENTS

No Amendment has been filed subsequent to the issuance of the Final Official Action mailed on March 29, 2011.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 28 is directed to a method of using an article having a nonfouling surface, said method comprising:

(a) providing an article having a nonfouling surface thereon, said article comprising:

(i) a substrate having a surface portion;

(ii) a linking layer on said surface portion; and

(iii) a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion; said brush molecule comprising a stem formed from the polymerization of said monomer core groups, and a plurality of branches formed from said protein-resistant head group projecting from said stem, and wherein said brush molecule is formed on said surface portion at a density from 40 to 100 milligrams per meter^2; and then

(b) contacting said article to a biological fluid, and where proteins in said fluid do not bind to said surface portion. *See, e.g.*, Specification at page 3, lines 2-12; page 11, lines 25-28; page 6, lines 10-13; page 8, lines 26-32; page 10, lines 10-16; and page 11, lines 19-22.

Independent Claim 51 is directed to a method of using an article having a nonfouling surface thereon, said method comprising:

(a) providing an article having a nonfouling surface thereon, said article comprising:

(i) a substrate having a surface portion;

(ii) a linking layer on said surface portion; and

(iii) a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion; said brush molecule comprising a stem formed from the polymerization of said monomer core groups, and a plurality of branches formed from said protein-resistant head group projecting from said stem, and wherein said brush molecule is formed on said surface portion at a density from 40 to 100 milligrams per meter^2; and then

(b) contacting said article to a biological fluid, and where proteins in said fluid do not bind to said surface portion;

wherein said contacting step is carried out *in vivo* or *ex vivo*; wherein said biological fluid consists essentially of blood, blood plasma, peritoneal fluid, cerebrospinal fluid, tear, mucus, or lymph fluid; and wherein said contacting step is carried out for a time period of at least one day. *See, e.g.*, Specification at page 3, lines 2-12; page 11, lines 25-28; page 6, lines 10-13; page 8, lines 26-32; page 10, lines 10-16; page 11, lines 19-22; page 11, line 28 to page 12, line 3; and page 5, lines 20-26.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are properly rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** in view of **Hawker et al.**, **Zhang et al.**, **Morgan**, **Allbritton et al.**, and **Leckband et al.**
2. Whether Claims 8 and 28 are properly rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** in view of **Hawker et al.**, **Zhang et al.**, **Morgan**, **Allbritton et al.**, and **Leckband et al.** and further in view of **Guan et al.**

ARGUMENT

I. The Standard of a *Prima Facie* Case of Obviousness Under 35 U.S.C. § 103(a)

A determination under 35 U.S.C. § 103(a) that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.* 810 F.2d 1593, 1 USPQ2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. After the facts are determined, the decision maker is tasked with the legal determination of whether the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time of invention. *Id.* at 1596.

"The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549 (Fed. Cir. 1985) (emphasis added). As clearly noted in *KSR International Co. v. Teleflex Inc., et al.*:

> [I]t can be important to identify a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does*. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

550 U.S. 398, 418-419 (2007) (emphasis added).

As stated in the recently published Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143).

First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some *suggestion or incentive that would have motivated* the skilled artisan to modify a reference or to combine references. See, e.g., *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986).

Second, the proposed modification or combination of the prior art must have a *reasonable expectation of success*, determined from the vantage point of the skilled artisan at the time the invention was made. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Third, the prior art reference or combination of references *must teach or suggest all of the limitations of the claims*. As was stated in the decision *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970), "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art."

The United States Patent and Trademark Office (USPTO) has the initial burden under § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The evidence of record must show that the legal determination of obviousness is more probable than not. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992); M.P.E.P. § 2142.

Appellant respectfully submits that a *prima facie* case of obviousness under 35 U.S.C. § 103(a) cannot be supported for want of an adequate showing that it was more probable than not that one of ordinary skill in the art at the time of invention would have combined the cited references to arrive at the claimed method in view of the art of record as a whole.

II. Rejection of Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 under 35 U.S.C. § 103(a)

As stated above, Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 stand finally rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** in view of **Hawker et al.**, **Zhang et al.**, **Morgan**, **Allbritton et al.**, and **Leckband et al.**

Independent Claim 28 recites as follows:

> 28. A method of using an article having a nonfouling surface thereon, said method comprising:
>
> *(a)* providing an article having a nonfouling surface thereon, said article comprising:
>
> *(i)* a substrate having a surface portion;
>
> *(ii)* a linking layer on said surface portion; and
>
> *(iii)* a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion;
>
> said brush molecule comprising a stem formed from the polymerization of said monomer core groups, and a plurality of branches formed from said protein-resistant head group projecting from said stem, and wherein said brush molecule is formed on said surface portion at a density from 40 to 100 milligrams per meter^2; and then
>
> *(b)* contacting said article to a biological fluid, and where proteins in said fluid do not bind to said surface portion.

Independent Claim 51 is also directed to a method of using an article having a nonfouling surface thereon, and recites the same elements as independent Claim 28 with the additional language "wherein said contacting step is carried out *in vivo* or *ex vivo*; wherein said biological fluid consists essentially of blood, blood plasma, peritoneal fluid, cerebrospinal fluid, tear, mucus, or lymph fluid; and wherein said contacting step is carried out for a time period of at least one day."

The Examiner argues in the Office Action of March 29, 2011 that it would have been obvious to one of ordinary skill in the art to combine the teachings of **six different** references,

Chapman et al., **Hawker et al.**, **Zhang et al.**, **Morgan**, **Allbritton et al.**, and **Leckband et al.**, to achieve the claimed method of using an article having a nonfouling surface thereon. As described in further detail below, Appellant submits that there is no suggestion or incentive to combine or modify the cited references and no reasonable expectation of success in making the combination or modification to arrive at the claimed method.

A. No Suggestion or Incentive for the Modification or Combination of References

There is no suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references in the manner suggested by the Examiner. Arguably, to arrive generally at the claimed brush polymer, the Examiner combines the teachings of Chapman et al., Zhang et al., and Hawker et al. Specifically, the Examiner alleges that it would have been obvious to prepare a polymer layer using acrylate monomers coupled to a protein resistant head group, as provided by Zhang et al., where the protein resistant head group is tri(sarcosine), as described by Chapman et al., via the method of Hawker et al. *See*, Office Action of March 29, 2011, page 8. Morgan, Leckband et al., and Allbritton et al. are cited as allegedly describing additional features of the claimed invention.

As demonstrated in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), analysis under 35 U.S.C. § 103 still requires a showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 n.3 (Fed. Cir. 2008). Moreover, "every limitation in the claim must be given effect rather than considering one in isolation from the others." *In re Geerdes*, 491 F.2d 1260, 1262-63 (CCPA 1974) (*emphasis added*). Thus, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (U.S. 2007) (*emphasis added*).

1. Proposed Modification of Zhang et al. is Contrary to Its Teachings

To begin, the Examiner cites **Zhang et al.** as allegedly teaching the claimed feature of the monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto. Specifically, the Examiner states that the polymers of Zhang et al. "are composed of monomers of methacryloyloxyethyl phosphorylcholine, an acrylate monomer with a coupled phosphorylcholine group, and butyl methacrylate ...." (Office Action of March 29, 2011, page 6). The Examiner arguably arrives at the brush molecules of the claimed method by combining Zhang et al. with Chapman et al. by "using an acrylate monomer coupled with tri(sarcosine) instead of the phosphorylcholine as taught by Zhang et al." (Office Action of March 29, 2011, page 8).

However, Zhang et al. is not directed to polymer brushes as in the claimed method nor is Zhang et al. directed to self-assembled monolayers (SAMs), as described in Chapman et al. Instead, Zhang et al. is directed to freestanding films or films coated on (essentially painted on) a surface. Specifically, Zhang et al. describes that PMB, a **pre-formed copolymer** (*i.e.*, a single pre-formed unit), was coated onto underlying matrices. *See*, p. 692, col. 1, first and second full paragraphs; col. 2, second paragraph; and Figure 1.

Thus, in order for the Examiner to meet this limitation of the claims, the pre-formed copolymer of Zhang et al. must be **broken down** into components comprising the acrylate monomer bound to phosphorylcholine. This is contrary to the teachings of Zhang et al. and this modification **changes the principle operation** of the polymer of Zhang et al. As provided in *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959), a showing of obviousness is insufficient when the proposed modification or combination of prior art changes the principle operation of the prior art invention being modified. *See*, MPEP 2143.01. In *In re Ratti*, the court held that the claims were not obvious, stating that the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." *Id.*, 270 F.2d at 813, 123 USPQ at 352.

The same is true here in that in order to allegedly arrive at the claimed brush polymer, the pre-formed copolymer of Zhang et al., one of the main references combined by the Examiner, must be substantially redesigned and constructed in a manner contrary to the teachings of Zhang et al. As discussed above, Zhang et al. is particularly cited by the Examiner to arrive at the claimed feature of the monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto. In order to meet the recitations of the claims, one would have to **break apart** the **pre-formed copolymer** of Zhang et al. into monomeric acrylate units (*i.e.*, specific pieces/components of the copolymer). Then, one would have to remove from the components of the copolymer only the acylated units bound to phosphorylcholine, of which there are only 0.3 mole fraction in the copolymer, in order to separate these units from the n-butyl methacrylate units, which do not contain phosphorylcholine. This modification **destroys** the pre-formed copolymer of Zhang et at. and would substantially alter the design of the elements in that it would no longer be pre-formed or a copolymer (*i.e.*, a single preformed unit). Moreover, there is no teaching or suggestion in the cited references to modify Zhang et al. in such a manner.

In fact, this modification to the copolymer of Zhang et al. would change the principle operation upon which the copolymer was designed to operate in that the **PMB copolymer itself** was determined to be a suitable material to use to construct membranes with a haemocompatible surface and **not** the phosphorylcholine bound acrylate monomers of the copolymer. *See*, Zhang et al., Abstract. The copolymer of Zhang et al. was selected based on its ability to mimic biological membranes, which have a hydrophilic portion and a hydrophobic portion, and Zhang et al. highlights that changes in the underlying material **greatly influence** the surface properties of the membranes. *See*, Zhang et al., Abstract. Thus, altering and/or removing portions of the copolymer would also likely greatly influence the surface properties of the membranes of Zhang et al. Further, as described in Zhang et al. at p. 699, the hydrophobic fatty acid chains of the co-polymer (*e.g.*, the n-butyl groups of the co-polymer) can affect the attachment, distribution, and

order of the copolymer on a particular substrate. Thus, removing this feature from the copolymer of Zhang et al. **destroys the principle operation** of the invention of Zhang et al.

Therefore, one of ordinary skill in the art would not be directed to modify Zhang et al. in the manner suggested by the Examiner since there is no suggestion to do so. Further, based on the teachings of Zhang et al. one of ordinary skill in the art would not only not expect the functionality of the polymers of Zhang et al. to be retained after being modified in such a manner, but also have no reasonable expectation of success since modifying the teachings of Zhang et al. in the manner suggested by the Examiner destroys the principal operation of the invention in Zhang et al. That is, it destroys the pre-formed copolymer determined by Zhang et al. to be able to form a suitable membrane with a haemocompatible surface. Accordingly, it is a clear factual error to modify Zhang et al. in the manner suggested.

Further, Zhang et al. alone or in combination fails to teach or suggest all aspects of the claimed invention. For instance, Zhang et al. fails to teach or suggest at least the following:

- that the polymer layer is formed on a linking layer by the process of surface-initiated polymerization of monomeric units,
- that the monomeric units comprise a vinyl monomer core group having at least one protein-resistant head group coupled thereto, and
- the claimed density of the brush molecule.

Thus, not only is the modification and combination of Zhang et al. with the cited references not appropriate, but also, there is no teaching or suggestion for making the proposed combination and modification.

2. Chapman et al. is Directed to a Different Type of Polymer

Further, the Examiner's reliance on **Chapman et al.** is based on an erroneous statement of fact in that Chapman et al. is not directed to brush polymers, as claimed, but instead to self-assembled monolayers (SAMs) on gold to provide reactive groups, to which a pre-formed polymer is then attached, and then to which protein resistant groups are in turn attached.

Appellant submits that the self-assembled monolayers of Chapman et al. are distinct from the brush polymers of the claimed method. As **the Examiner recognizes** on page 5 of the Office Action of March 29, 2011, Chapman et al. does not teach or suggest that the polymer layer is formed on the linking layer by the process of surface-initiated polymerization of monomeric units. Nor does Chapman et al. teach or suggest that the monomeric units comprise a vinyl monomer core group having at least one protein-resistant head group coupled thereto. As provided by Claims 28 and 51, it is these features of the polymer layer that form the claimed brush molecule on the surface portion of the substrate. Thus, contrary to the Examiner's assertions, Chapman et al. does not teach or suggest the claimed polymer brushes. Further, Chapman et al. also fails to teach or suggest the claimed density of the brush molecule.

3. Combination of References Fails to Correct the Deficiencies

The combination of Chapman et al. with the other cited references fails to correct the deficiencies mentioned above. For example, there is no teaching or suggestion to combine **Hawker et al.** with the cited references in the manner suggested by the Examiner. The Examiner combines the teachings of Chapman et al. and Hawker et al. "because both teach surface bound polymeric coatings attached via self assembled monolayers of reactive alkanethiol groups on metallic surfaces." (Office Action of March 29, 2011, pages 7-8). However, there is no teaching or suggestion in either Chapman et al. or Hawker et al. that the functional groups taught by Chapman et al. would work via the method of Hawker et al. to provide an article having a nonfouling surface of the claimed method.

Hawker et al. is directed to growing a film *in situ* on a surface, and does not suggest applying protein-resistance to a surface. Moreover, the combination of Chapman et al. and Hawker et al. **fails** to teach or suggest the claimed polymer layer. Instead, if one of ordinary skill in the art were to combine the teachings of Chapman et al. and Hawker et al., one would prepare the polymers of Hawker et al., and to add the functional groups taught by Chapman et al., one would then covalently graft onto the surface of the polymers of Hawker et al. a thin polymer film

layer. Then, as described in Chapman et al., this polymer film layer would be functionalized with a biologically resistant group. Thus, one would **not** arrive at the claimed polymer layer formed on a linking layer by the process of surface-initiated polymerization of monomeric units, wherein the monomeric units comprise a vinyl monomer core group having at least one protein-resistant head group coupled thereto to achieve the claimed density of the brush molecule. This is true even if the teachings of Zhang et al. are added to the combination, since adding an acrylate monomer coupled to phosphorylcholine or a copolymer to a polymer film layer does **not** achieve the brush molecule of the claimed method.

The other references cited by the Examiner, Morgan, Allbritton et al., and Leckband et al., also fail to correct these deficiencies.

Morgan is cited by the Examiner simply as describing a dental implant for *in vivo* contacting with blood, but also fails to teach or suggest the claimed article having a nonfouling surface thereon, yet alone a nonfouling surface comprising a brush polymer.

Allbritton et al. and **Leckband et al.** were cited by the Examiner as allegedly teaching the claimed density. However, Leckband et al. fails to teach or suggest the claimed brush polymer density, and, once again, Allbritton et al. is not directed to brush molecules, but rather to graft polymers. Appellant submits that not only are the graft polymers described in Allbritton et al. a **different** type of polymer than the claimed brush polymers, but also that the graft polymers of Allbritton et al. are formed by a **different method** than the claimed method. Specifically, the graft polymers of Allbritton et al. are covalently attached to a polymer substrate surface by ultraviolet graft polymerization. *See*, Allbritton et al., Abstract. As shown in Figure 1 and described at paragraph [0048], the monomers described in Allbritton et al. are grafted onto the polymer backbone of the polymer substrate surface.

In contrast, the claimed method comprises an article having a nonfouling surface thereon, wherein the article comprises a substrate have a surface portion, a linking layer on said surface portion, and a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a

vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion.

Appellant submits that contrary to the Examiner's contentions in regard to **Ikada et al.**[1] that "graft polymerization onto a surface creates initiating functional groups on the surface" (*See*, Office Action at page 12), the methods and subsequent products of Allbritton et al. and the claimed subject matter are still **different**. While the methods may be similar in one aspect, it does not change the fact that the graft polymers of Allbritton et al. are covalently attached to a polymer substrate surface by ultraviolet graft polymerization. It is factually incorrect to equate overall different methods resulting in different products based on one similar feature. Further, contrary to the Examiner's contentions, the nature of the substrate can alter to the final polymer product. This was clearly demonstrated in Zhang et al. in which changes in the underlying material **greatly influenced** the surface properties of the membranes, and confirms that the Examiner's statements are erroneous statements of fact. *See*, Zhang et al., Abstract.

Allbritton et al. does not teach or suggest a linking layer on the surface portion. Instead, Allbritton et al. describes covalent attachment of the monomers directly to the surface of the substrate. *See*, Allbritton et al., Figure 1 and paragraph [0018]. Further, Allbritton et al. fails to teach or suggest a polymer layer formed on the linking layer, yet alone a polymer formed on the linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion. Once again, as provided by Claims 28 and 51, it is these features of the polymer layer that form the claimed brush molecule on the surface portion of the substrate with the claimed density.

Thus, the graft polymers described in Allbritton et al. are not only **different** from the claimed brush polymers, but also formed by a **different** process. Accordingly, there is no

[1] Ikada et al. was not formally cited in the rejection of the above-referenced claims. Instead, Ikada et al. was cited in support of the Examiner's argument in regard to Allbritton et al. and referenced on page 12 of the Office Action mailed on March 29, 2011 in the Examiner's response to the Applicant's arguments.

teaching or suggestion that would have motivated one of ordinary skill in the art to combine the density of the polymers of Allbritton et al. with the above cited references to achieve the claimed brush polymer density. Further, given these differences, there would be no reasonable expectation of success.

The obligatory legal standard, as provided under *KSR*, is that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *P&G v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (*emphasis added*). The mere possibility that one of ordinary skill in the art could modify the cited references to arrive at the claimed invention, without any suggestion for making the proposed modification, is insufficient. A hindsight comparison selecting *isolated* features from references directed to *different* types of polymers is the only way in which such a combination of references could be combined to arguably arrive at the claimed invention, which is *improper*.

Again, the fact that the invention employs known elements does not preclude patentability. It is the claimed combination of elements which is the proper basis for review. "Virtually all inventions are necessarily combinations of old elements." *Panduit* at 1575 (citing *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 220 USPQ 97, 99-100 (Fed. Cir. 1983)). Indeed, the Federal Circuit has stated (in regard to an obviousness-type invalidity challenge to an issued patent) that "[t]he notion, therefore, that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, §103." *Panduit* at 1575.

Given the discussion above, Appellant submits that there is no teaching or suggestion to combine the cited references to arrive at the claimed method. Thus, Appellant submits that the claimed method is patentable over the cited references.

B. No Reasonable Expectation of Success

Appellant further submits that given the differences described above between the cited references and the claimed subject matter, there also is no reasonable expectation of success in making the proposed combination to arrive at the claimed subject matter.

For example, the claimed brush polymer is formed via reactions that are chosen to result in a relatively high density polymer immobilization. One of ordinary skill in the art following the cited references would **not** arrive at such a high density immobilization because it would result in a relatively low "excluded volume" per immobilized chain. For example, Zhang et al. specifically immobilizes non-fouling moieties on a surface and does so at a relatively low density. In that literature, it was believed that such polymers exhibited non-fouling properties partly due to a high degree of chain flexibility/mobility, which results in a relatively large "excluded volume" (*i.e.*, the volume that the chain functionally occupies). Accordingly, it would have been **counter-intuitive** to follow the cited references to create a high density of immobilized chains bearing non-fouling moieties, with a relatively low excluded volume per chain, as such a polymer would **not** have been indicated to result in an enhancement of the non-fouling properties. Thus, based on the teachings of the cited references there would be no reasonable expectation of success in arriving at the claimed method comprising a nonfouling surface with high density polymer immobilization.

Moreover, assuming for the sake of argument that the combination of the cited references is appropriate and there is a some suggestion for making the combination, there would be no reasonable expectation of success that the protein-resistant groups of Chapman et al. would work with the acrylate monomers of Zhang et al. in the method of Hawker et al. to achieve the claimed brush molecule with the density described in Leckband et al. and Allbritton et al. to provide the claimed article, such as an orthopedic implant as described by Morgan, as the Examiner alleges. For example, in order to arrive at the claimed high density brush molecule, high molecular weight polymers are formed on the surface **monomer by monomer**. Thus, like building blocks, each individual monomer is added to the end of the prior added monomer to **form** a high density

of high molecular weight polymers. This is **contrary** to the teachings of the cited references, which are directed to a **different** method in that they utilize a "**grafted to**" method where either small molecule thiols or high molecular weight polymers are grafted **onto** a surface. One of ordinary skill in the art at the time of the invention would not have a reasonable expectation of success in arriving at the claimed method given the teachings of the cited references and the differences between the polymers of the cited references and the claimed brush polymers.

Finally, Appellant submits that the Examiner's contention that "it would have been well within the purview of one of ordinary skill in the art to optimize the graft density of the polymers" is insufficient to support a rejection under 35 U.S.C. § 103. Looking to guidance from the case law, in the recently-decided case of *In re Kubin*, 561 F.3d 1351, 1359 (2009), the Federal Circuit explained two situations in which "obvious to try" is not sufficient to support a rejection under § 103. These two situations were as follows:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful

and

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it (quoting *In re O'Farrell*, 853 F.2d 894,903 (Fed. Cir. 1988). *Id.* at 1359.

Appellant submits that, as described above, in order to arrive at the claimed invention one of ordinary skill in the art would have to vary all parameters with no direction for the modifications. That is, in the combination of references proposed by the Examiner, one of

ordinary skill in the art would have change both the type of polymer and the method by which the polymer was formed in order to arrive at the claimed high density brush molecule. This is insufficient to support a rejection under 35 U.S.C. § 103. Appellant further submits that *at best*, the cited references *merely suggest the exploration* of a field of experimentation with respect to the claimed brush molecule and that this also is insufficient as a matter of law to support a rejection under 35 U.S.C. § 103.

Given the discussion above, Appellant submits that there also is no reasonable expectation of success in making the proposed combination to arrive at the claimed subject matter. Thus, Appellant submits that the claimed method is patentable over the cited references.

III. Rejection of Claims 8 and 28 under 35 U.S.C. § 103(a)

Claims 8 and 28 stand finally rejected under 35 U.S.C. § 103(a) based on **Chapman et al.** in view of **Hawker et al.**, **Zhang et al.**, **Morgan**, **Allbritton et al.**, and **Leckband et al.** as applied to Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63, and further in view of **Guan et al.** (U.S. Patent No. 6,071,980). **Guan et al.** is directed to a process for the polymerization of vinyl monomers by atom transfer radical polymerization using a first compound containing a transition metal and a second compound capable of radically transferring an atom or group to the first compound. However, Guan et al. fails to correct the deficiencies discussed above for the combination of Chapman et al., Hawker et al., Zhang et al., Morgan, Allbritton et al., and Leckband et al.

1. Guan et al. alone or in combination with the cited references fails to teach or suggest all elements of Claim 28

Specifically, for Claim 28, Guan et al. alone or in combination with the cited references fails to teach or suggest at least the following claimed features:

- that the polymer layer is formed on a linking layer by the process of surface-initiated polymerization of monomeric units,

- that the monomeric units comprise a vinyl monomer core group having at least one protein-resistant head group coupled thereto, and
- the claimed density of the brush molecule.

For at least these reasons, Appellant submits that Claim 28 is patentable over the cited references.

2. Guan et al. alone or in combination with the cited references fails to teach or suggest all elements of Claim 8

In regard to Claim 8, Guan et al. is directed to a different type of atom transfer radial polymerization than the claimed polymerization, and thus results in a different product. For instance, the claimed polymerization is a **surface-initiated** atom transfer radical polymerization. There is no mention or suggestion in Guan et al. of performing the polymerization on a surface or other substrate. This is clearly seen in the examples of Guan et al., which all describe polymerization of the polymer **in solution** and recovery via **precipitation and/or filtration**. A **precipitate from solution** is in fact a completely different product than the claimed brush polymer, which is formed on a surface at a density from 40 to 100 milligrams per meter^2. Thus, there is no teaching or suggestion in Guan et al. of the claimed surface-initiated atom transfer radical polymerization. Further, as mentioned above, there is no teaching or suggestion in Guan et al. of a vinyl monomer core group having at least one protein-resistant head group coupled thereto.

Moreover, Guan et al. provides no reasonable expectation of success to make the proposed combination or modification in order to arrive at the claimed brush polymer, which is a different product than the product described by Guan et al. Therefore, based on Guan et al. alone or in combination with the cited references, there is no reasonable expectation of success that one of ordinary skill in the art would arrive at the claimed brush polymer.

Accordingly, Appellant submits that there is no teaching or suggestion to combine Guan et al. with the other cited references and no reasonable expectation of success to arrive at the

brush polymer of the claimed method. Thus, Appellant submits that Claim 8 is patentable over the cited references.

IV. The Dependent Claims Are Patentable

The dependent claims are patentable at least per the patentability of the respective ones of independent Claims 28 and 51 from which they depend.

V. Conclusion

On the entire record and in view of all the cited references, Appellant submits that Claims 2, 4-9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are patentable under 35 U.S.C. § 103(a). Accordingly, it is respectfully requested that the Examiner's conclusions be reversed, and that this case be passed to issuance.

Respectfully submitted,

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CLAIMS APPENDIX

1. (Cancelled).

2. (Previously presented) The method of claim 28, wherein said surface portion comprises a material selected from the group consisting of metals, metal oxides, semiconductors, polymers, silicon, silicon oxide, and composites thereof.

3. (Previously presented) The method of claim 28, wherein said surface portion comprises a material selected from the group consisting of polymers, silicon, silicon oxide, and composites thereof.

4. (Previously presented) The method of claim 28, wherein said linking layer is continuous.

5. (Previously presented) The method of claim 28, wherein said linking layer is patterned.

6. (Previously presented) The method of claim 28, wherein said linking layer is a self-assembled monolayer.

7. (Previously presented) The method of claim 28, wherein said linking layer comprises an initiator-terminated alkanethiol.

8. (Previously presented) The method of claim 28, wherein said surface-initiated polymerization is carried out by atom transfer radical polymerization.

9. (Previously presented) The method of claim 28, wherein said surface-initiated

polymerization is carried out by free radical polymerization.

10. (Cancelled)

11. (Previously presented) The method of claim 28, wherein said vinyl monomer is selected from the group consisting of styrenes, acrylonitriles, acetates, acrylates, methacrylates, acrylamides, methacrylamides, vinyl alcohols, vinyl acids, and combinations thereof.

12. (Previously presented) The method of claim 28, wherein said protein resistant head group comprises a hydrophilic head group.

13. (Previously presented) The method of claim 28, wherein said protein resistant head group comprises a kosmotrope.

14. (Previously presented) The method of claim 28, wherein said protein resistant head group is selected from the group consisting of oligosaccharides, tri(propyl sulfoxide), phosphorylcholine, tri(sarcosine) (Sarc), N-acetylpiperazine, permethylated sorbitol, hexamethylphosphoramide, an intramolecular zwitterion, and mannitol.

15. (Previously presented) The method of claim 28, wherein said protein resistant head group comprises poly(ethylene glycol).

16. (Previously presented) The method of claim 28, wherein said brush molecule is from 5 to 50 nanometers in length.

17. (Cancelled)

18. (Previously presented) The method of claim 28, further comprising a protein, peptide, oligonucleotide or peptide nucleic acid covalently coupled to said brush molecule, said protein, peptide, oligonucleotide or peptide nucleic acid consisting essentially of a single preselected molecule.

19. (Previously presented) The method of claim 18, wherein said preselected molecule is a receptor.

20. (Previously presented) The method of claim 28, wherein said article is a contact lens or intra-ocular lens.

21. (Previously presented) The method of claim 28, wherein said article is an orthopedic implant.

22. (Previously presented) The method of claim 28, wherein said article is a vascular graft or a stent.

23. (Previously presented) The method of claim 28, wherein said article is a shunt or catheter.

24. (Previously presented) The method of claim 28, wherein said article is a dialysis machine or blood oxygenator and said surface is a blood contact surface.

25. (Previously presented) The method of claim 28, wherein said article is an implantable electrical lead, an implantable electrode, an implantable pacemaker, or an implantable cardioverter.

26. (Previously presented) The method of claim 28, wherein said article is a label-free optical or mass detector and said surface is a sensing surface.

27. (Previously presented) The method of claim 28, wherein said article is a biosensor or assay plate.

28. (Previously presented) A method of using an article having a nonfouling surface thereon, said method comprising:

(a) providing an article having a nonfouling surface thereon, said article comprising:

(i) a substrate having a surface portion;

(ii) a linking layer on said surface portion; and

(iii) a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion;

said brush molecule comprising a stem formed from the polymerization of said monomer core groups, and a plurality of branches formed from said protein-resistant head group projecting from said stem, and wherein said brush molecule is formed on said surface portion at a density from 40 to 100 milligrams per meter^2; and then

(b) contacting said article to a biological fluid, and where proteins in said fluid do not bind to said surface portion.

29. (Original) The method of claim 28, wherein said contacting step is carried out *in vivo* or *ex vivo*.

30. (Original) The method of claim 28, wherein said biological fluid consists essentially of blood, blood plasma, peritoneal fluid, cerebrospinal fluid, tear, mucus, or lymph fluid.

31. (Original) The method of claim 28, wherein said contacting step is carried out for a time period of at least one day.

32-50. (Cancelled)

51. (Previously presented) A method of using an article having a nonfouling surface thereon, said method comprising:

(a) providing an article having a nonfouling surface thereon, said article comprising:

(i) a substrate having a surface portion;

(ii) a linking layer on said surface portion; and

(iii) a polymer layer formed on said linking layer by the process of surface-initiated polymerization of monomeric units thereon, with each of said monomeric units comprising a vinyl monomer core group having at least one protein-resistant head group coupled thereto, to thereby form a brush molecule on said surface portion;

said brush molecule comprising a stem formed from the polymerization of said monomer core groups, and a plurality of branches formed from said protein-resistant head group projecting from said stem, and wherein said brush molecule is formed on said surface portion at a density from 40 to 100 milligrams per meter^2; and then

(b) contacting said article to a biological fluid, and where proteins in said fluid do not bind to said surface portion;

wherein said contacting step is carried out *in vivo* or *ex vivo*; wherein said biological fluid consists essentially of blood, blood plasma, peritoneal fluid, cerebrospinal fluid, tear, mucus, or lymph fluid; and wherein said contacting step is carried out for a time period of at least one day.

52. (Previously presented) The method of claim 51, wherein said article is a contact lens or intra-ocular lens.

53. (Previously presented) The method of claim 51, wherein said article is an orthopedic implant.

54. (Previously presented) The method of claim 51, wherein said article is a vascular graft or a stent.

55. (Previously presented) The method of claim 51, wherein said article is a shunt or catheter.

56. (Previously presented) The method of claim 51, wherein said article is a dialysis machine or blood oxygenator and said surface is a blood contact surface.

57. (Previously presented) The method of claim 51, wherein said article is an implantable electrical lead, an implantable electrode, an implantable pacemaker, or an implantable cardioverter.

58. (Previously presented) The method of claim 51, wherein said article is a label-free optical or mass detector and said surface is a sensing surface.

59. (Previously presented) The method of claim 51, wherein said article is a biosensor or assay plate.

60. (Previously presented) The method of claim 28, wherein the contacting step is carried out for a time period of up to one month.

61. (Previously presented) The method of claim 51, wherein the contacting step is carried

out for a time period of up to one month.

62. (Previously presented) The method of claim 28, wherein the contacting step is carried out for a time period of up to approximately 26 days.

63. (Previously presented) The method of claim 51, wherein the contacting step is carried out for a time period of up to approximately 26 days.

EVIDENCE APPENDIX

NONE

RELATED PROCEEDINGS APPENDIX

NONE